ORIGINAL ARTICLE

Does human milk reduce infection rates in preterm infants? A systematic review

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One of the reasons for advocating human milk (HM) feeding for preterm infants is the belief that this provides the infant with a degree of protection from infection. Providing fresh HM for such infants is challenging for mothers and staff, and consequently it is important that its benefits are rigorously evaluated. Therefore a systematic review was undertaken to assess all publications concerned with human milk feeding and infection in very low birth weight (VLBW) preterm infants. Nine studies—six cohort and three randomised controlled trials (RCT)—were assessed using predefined criteria. Methodological problems included poor study design, inadequate sample size, failure to adjust for confounding variables, and inadequate definitions of HM feeding and outcome measures. In conclusion, the advantage of HM in preventing infection in preterm, (VLBW) infants is not proven by the existing studies. Recommendations are made regarding the methodology required for further study of this important topic.

Among the reasons used to advocate feeding preterm low birth weight infants human milk (HM) is the belief that HM is advantageous in reducing infections when compared to preterm formula. Protective effects of breast feeding in reducing sepsis and diarrhoea in term infants and children have been reported in developing countries.[1–3] Furthermore, breast milk has anti-infective properties due to the high content of IgA, lysozyme, lactoferrin, and interleukins.[4 5] Non- pathogenic maternal bacteria transmitted via breast milk and skin to skin contact may promote enteromammary immune responses.[6] Biochemical and microbiological studies suggest that these properties apply to preterm as well as term HM feeding.[4 7] In practice preterm infants are subjected to HM feeding in varying proportions. Assessment of anti-infective benefits of HM is complicated by the impact of heat treatment, which is known to alter the immunological properties of milk,[8] the practice of providing donor milk, and the methods of delivery and storage, which may include freezing.[9] Furthermore, providing preterm infants with an adequate supply of good quality breast milk takes enormous commitment from both mothers and professionals,[10] especially if fresh raw mother's milk is required. Consequently it is important that the benefits of HM in reducing infections are fully evaluated, especially as infections are a major cause of morbidity and mortality in preterm, very low birth weight (VLBW), and extremely low birth weight (ELBW) infants.[11 12] The purpose of this paper is to review the scientific evidence to determine whether human milk feeding protects against infection in preterm infants >1500 g (VLBW) and >1000 g (ELBW) infants. Necrotising enterocolitis was excluded from this review, because the relation with infection is not entirely clear and this outcome has already been the subject of a systematic review.[13]

SELECTION OF STUDIES

Medline, Embase, Cinahl databases, and the Cochrane controlled trials register were systematically searched for publications from 1970 to 2003, using text words and subject headings (MeSH). References from previous reviews and other relevant studies were also examined. Fourteen studies that listed infection as an outcome of feeding HM (fortified or unfortified) versus artificial formula in preterm, VLBW infants were identified. No language restrictions were applied. Five of these studies were excluded for the following reasons: two studies did not specify birth weights,[14 15] two studies assessed only infants >1500 g,[16 17] and one study did not include infection as an independent outcome measure.[18]

Nine studies—three randomised controlled trials (RCTs)[19–21] and six cohort studies[22–27] matched the prespecified criteria. The studies could not be limited to only VLBW infants, since six publications[19–21 26 27] included some infants >1500 g. Each study was evaluated for definitions of HM feeding, assessment of outcomes, potential confounding factors, and statistical analysis and power.[28]

OVERVIEW OF STUDIES

Table 1 shows the characteristics of the nine studies. The three RCTs were carried out in India from 1980 to 1984 while the six observational studies were prospective cohort studies from the USA, UK, Australia, and Mexico. A total of 1131 infants—769 infants from cohort studies and 362 from randomised trials—were assessed (fig 1); 86.4% of infants in the cohort studies were <1500 g, while 13.8% were <1500 g in the RCTs. All studies concluded that HM feeding had a protective effect in reducing infections in preterm, low birth weight infants.

CLASSIFICATION OF HM FEEDING

A major flaw noted in all the studies was the lack of a consistent definition of HM fed groups or methods used to quantify HM intake. Despite the current practice in most hospitals of providing any available HM to infants, the imprecise categorisation of feeding—that is, grouping infants with differing degrees of HM intake together, reduces the scientific validity of studies. Further, the true effect of HM may be grossly underestimated because of the varied definitions of HM feeding used in these studies. Exclusive HM feeding (with or without preterm fortifier) was reported in only 86 (11.1%) infants in the cohort studies and 113 infants (31.2%) in RCTs. It was not possible to ascertain the number of infants <1500 g who were exclusively HM fed in

Abbreviations: ELBW, extremely low birth weight; HM, human milk; RCT, randomised controlled trial; UTI, urinary tract infection; VLBW, very low birth weight

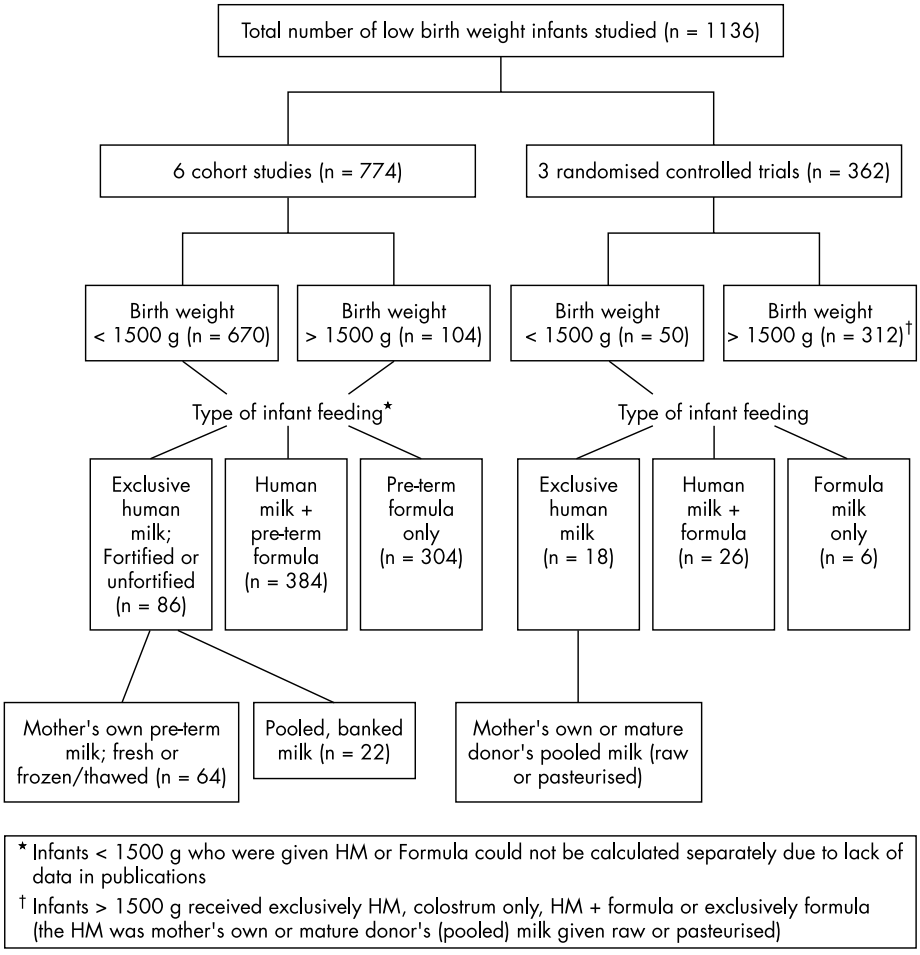

Figure 1 Total number of infants in studies broken down according to study type, birth weight, and type of feed received.

the cohort studies, but only 18 infants were exclusively HM fed in the RCTs (fig 1). The remaining ''HM fed'' infants in all studies received a combination of HM and formula with large variations in the proportions of each (table 1). The type of HM too differed between studies (fig 1), causing further confusion in interpretation of results since the effect of storage and processing on HM are diverse.[29] In the RCTs too, HM groups varied from infants given only colostrum and formula milk[20] to others fed unknown amounts of raw or pasteurised, pooled, HM.[19 21] A further problem with definitions is illustrated by a study where the HM fed group were infants who had 40% of enteral intake as HM.[22] This definition is flawed because smaller weaker infants receiving primarily intravenous nutrition with minimal enteral intake may be wrongly classified in the higher HM categories. The duration of HM feeding was not mentioned or taken into account in five studies,[19–21 25 26] and subgroup analysis of different birth weight groups was not reported in any.

OUTCOME MEASURES

Sepsis was the main outcome measure examined in four cohort studies, while one assessed necrotising enterocolitis, urinary tract infections (UTI), and diarrhoea[27] (table 1). One long term follow up study examined a range of infections including coryza, otitis media, and bronchiolitis.[26] Most investigators used uniform criteria such as clinical signs and positive blood cultures to diagnose sepsis. However, interpretation of both laboratory results and clinical signs presents difficulties when diagnosing sepsis in preterm infants,[30] especially as the severity of illness was not considered in any of the studies. The majority of neonatal sepsis such as bacteraemia and pneumonia is ill defined and consequently very precise diagnostic definitions are required to ensure accuracy of outcome measures in a study. Grouping all infection together as an outcome measure also presents problems since diagnostic criteria and clinical implications are obviously different for infections such as meningitis, urinary infection, and diarrhoea. Furthermore, any protective effect confined to a certain type of infection may be masked. Two cohort studies attempted to diagnose UTI, diarrhoea, or other infections, but the results proved difficult to interpret since one study did not provide any information on how infections were diagnosed or the duration of HM feeding.[27] The results of the other study, which included 24 HM fed infants, were entirely dependent on subjective parental reporting of duration of upper respiratory symptoms.[26] If formula fed infants have an increased rate of clinically significant infections, they might be expected to have a longer hospital stay. The duration of hospital stay was assessed in six studies in relation to the type of milk intake, but a significant difference was found in only one of these studies.[23] The RCTs reported on a range of infections including sepsis, diarrhoea, conjunctivitis, thrush, and pyoderma, but similar problems in confirming infections also applies to these studies.

HM FEEDING AND INFECTION

An infant is most susceptible to infection during the early neonatal period when enteral intake is minimal or non-existent.[31] Therefore averaging HM intake for the entire study period and then comparing infection rates as done by some investigators,[23 25–27] will obscure the true picture, even though

Table 1 Characteristics and results of studies

First author, location, and study type	n	Study period	Definition of human milk (HM) intake	Statistical analysis and outcome	Confounding factors	Major problems*
El Mohandes,[20] USA, cohort	T 173† I 59 C 114	0–38 days	HM only as enteral nutrient ⩾1 week or as 40% of enteral calorie intake + FM	Survival analysis using time to infection: lower incidence of sepsis in HM group; OR = 0.38‡, CI = 0.05–0.95§, p = 0.04	None mentioned or controlled	Flawed definition of HM feeding No exclusively HM fed group Infection severity not assessed
Schanler,[21] USA, cohort	T 108 I 62 C 46	0–9 weeks	>50 ml/kg/day HM averaging through hospital stay + FM	Logistic regression: lower proportion of sepsis episodes in HM group; OR = 0.46, CI = 0.24–0.87, p = 0.016	Controlled: antenatal steroid exposure Not controlled: maternal education, maternal contact and holding, milk intakes	No subgroup analysis of exclusive HM fed group Severity of infection not assessed Important confounders not controlled
Furman,[22] USA, cohort	T 119 I 79 C 40	0–6 weeks	Graded doses 1–24, 25–49, ⩾50 ml/kg HM through week 4 + FM	Poisson regression analysis: lower number of sepsis episodes in ⩾50 ml/kg HM group; RR = 0.27, CI = 0.08–0.95, p<0.05	Controlled: birth weight, gender, ethnicity Not controlled: dexamethasone	No exclusive HM fed group Severity of infection not assessed Important confounder not controlled
Hylander,[23] USA, cohort	T 212 I 123 C 89	Hospital stay	Any amount of HM+FM Duration unknown	Logistic regression on selected group of measured variables: lower odds of infection in HM groups; OR = 0.46, CI = 0.24–0.87, p = 0.016	Controlled: maternal sociodemographic factors, birth weight, 5 minute Apgar, days of mechanical ventilation	Flawed definition of HM feeding No exclusive HM fed group Severity of infection not assessed, duration of feeding unknown
Blaymore-Bier,[25] Australia, cohort	T 39 I 24 C 15	1, 3, 7, 12 months	Any amount of HM+FM up to 1 year	ANCOVA: lesser days of URTI symptoms at: 1 month, p = 0.02, and 7 months, p = 0.006	Controlled: socioeconomic status	Small numbers with only 5 infants exclusively HM fed Bias in detecting outcome
Contreras-Lemus,[24] Mexico, cohort	T 118 I 59 C 59	Hospital stay	Preterm HM only Duration unknown	χ^2 Lower incidence of diarrhoea; RR¶ = 9, and urinary infection; RR5 in HM group, p<0.01	None mentioned or accounted for	No details of diagnosis of outcome measures. Duration of feeding unknown
Narayanan,[17] India, RCT	T 70 I 32 C 38	Hospital stay	EBM (mother's own or mature donor) + FM Duration unknown	χ^2 test Lower infection rate in HM group (n = 9), FM (n = 24), p<0.01	None mentioned or accounted for	Small numbers with only 5 infants <1500 g Flawed definition of HM feeding, duration unknown Lack of exclusive HM fed group
Narayanan,[18] India, RCT	T 66 I 33 C 33	Hospital stay	Colostrum 10 ml TDS (mother's own or mature donor) + FM Duration unknown	χ^2 test Lower infection rate in HM group (n = 7), FM (n = 18), p<0.01	None mentioned or accounted for	Small numbers with only 5 infants <1500 g Flawed definition of HM feeding, duration unknown Lack of exclusive HM fed group
Narayanan,[19] India, RCT Narayanan	T 226 I 169	Hospital stay	Raw or pasteurised EHM (mother's own or mature donor) Duration unknown	χ^2 test Greater infection rate pasteurised HM + FM group 33.3%, raw HM group: 10.5%, p<0.05	None mentioned or accounted for	Inadequate numbers with only 20 infants <1500 g No exclusively formula fed group** Duration of HM feeding unknown

*No precalculation of sample size in any study.
†T, total number in study; I, number in intervention group; C, number in control group.
‡OR, odds ratio.
§CI, 95% confidence interval.
¶RR, relative risk.
**All control infants were exclusively fed formula milk (FM), except in Narayanan *et al*[19] where the control group was given pasteurised HM + formula milk.

there may be some value in a minimal HM intake during the initial few days. The precise timing of infections in relation to start of enteral feeding (whether infants in formula groups developed infections sooner than HM groups, and the effects on infection rates once HM feeding was discontinued) was not examined in any study. Though a dose-response effect was assessed in two studies,[24 25] only one study showed that the lowest rates of sepsis were in infants consuming ⩾50 ml/kg/day of HM,[24] while any amount of HM seemed adequate to lower infection rates in the other study.[25]

POTENTIAL CONFOUNDING VARIABLES AND STATISTICAL ANALYSIS

From a statistical perspective, most cohort studies showed bias in favour of HM groups in terms of higher maternal sociodemographic variables (table 1). These included greater avoidance of alcohol, smoking, and illegal drug taking and better antenatal care during the prenatal period. Some HM fed groups also had more maternal visits and contact with mothers, differences in duration of oxygen or steroid therapy, and higher milk intakes.[23 24] There are also many other risk factors that may predispose an infant to late onset sepsis including parenteral lipids, male gender, duration of antibiotic use, and H_2 antagonists.[32–34] Four cohort studies[23–25 27] attempted to account for at least some variables, whereas two studies neglected to adjust for any confounding factors in the analysis[22 26] (table 1). No study attempted any form of matching in order to eliminate the most important confounding variables. However, some of the studies were too small to make this possible.[19 22 26 27] Consequently results must be interpreted cautiously, since adjustment for covariates may change differences in infection rates between HM and formula fed infants.

The authors' conclusions from all nine studies indicate that HM had a protective effect in reducing infection when compared with formula milk (table 1). HM feeding did not increase infection rates in any study. If the results are taken at face value they are very encouraging. One trial reported 0.3 ± 0.5 episodes of sepsis/infant in the HM group and 0.6 ± 0.7 episodes/infant in the formula group, while in another, the HM group had 0.09 episodes of sepsis/infant and the formula group had 0.4 episodes/infant during the study period.[23 24]

CONCLUSIONS

There are serious methodological flaws in all of the cohort studies which include poor study design, inadequate sample sizes, neglecting to account for some confounders, failure to eliminate the effects associated with maternal choice of feeding method, and other maternal sociodemographic variables (table 1). Definitions of HM feeding and outcome measures were inconsistent and inadequate. All studies reviewed in this paper, including the RCTs, used arbitrary sample sizes without prestudy power calculation. Many reviews have quoted the three RCTs as sound evidence that HM protects preterm, VLBW infants from infection. However, in these three trials, only 50 VLBW infants in total were studied and of these, only 18 exclusively HM milk fed. No ELBW infants were included. Clearly there is a possibility of imbalances between covariates in two groups with small sample sizes, even when the groups are selected using randomisation. Further, these studies were carried out in a developing country with a greatly different infection risk when compared to developed countries, at a time when preterm formulae were not developed and lacked essential nutrients specifically designed for preterm infants.[35] Therefore, generalisation of these results to include all VLBW infants would not be appropriate. Therefore, benefits of HM feeding in preventing infection in preterm, VLBW infants is not conclusively proven by the currently available evidence.

FUTURE RESEARCH

As the value of HM feeding in preventing infection in preterm infants remains uncertain, further study is recommended. The greatest barrier to collecting evidence regarding effects of HM on infection is the impossibility of carrying out an RCT for ethical reasons. To calculate sample sizes for a future study we have used data from one RCT[19] (table 1). The primary outcome in this trial was infection rates: raw HM group, n = 6 (10.5%); formula milk + pasteurised HM group, n = 19 (33.5%). In order to detect this difference in a future study of independent groups with 90% power and two sided significance of 5%, 64 are required in each group with an addition for dropout. Since an RCT is not possible, it is likely that imbalances between the groups would be observed. Logistic regression could be used to adjust for any imbalances, but the addition of covariates would inflate the sample size of 128 described above. Alternatively a matched pairs design could be used. In this case, using the same proportions a total of 47 discordant pairs, leading to a sample size of 127 pairs plus an addition for dropout, would be required for 90% power and two sided significance of 5%.

HM feeding and outcome measures must be adequately defined. We suggest that HM feeding should be defined as total oral feeding, exclusively with mother's own breast milk for the study period. New techniques in breast massage and pumping would make this a viable proposition.[36] HM fortifiers must be accepted, as they are often required to ensure adequate growth.[37] Assessment of infection should begin with the onset of milk feeds and a detailed, precise record of milk intake and duration of HM feeding is essential.

The primary outcome must be a common event. Preterm infants frequently have courses of antibiotics for nonspecific, general, or respiratory deterioration. Using such events would require rigorous evaluation using predefined criteria to determine inclusion as an episode of sepsis. These criteria should take account of illness severity, inflammatory markers, changes in cell counts, culture results, and response to antibiotics. No evaluation is 100% discriminatory, but would be valid if applied equally to both groups. Clearly, all episodes of clearly defined infection, such as staphylococcal skin infection or meningitis, should also be recorded.

The length of the study should probably equate with the period when infants are at the greatest risk of infection. Neonatal human milk feeding may have long lasting benefits during the first year of life, but as the infections encountered are different, a separate long term follow up protocol would be required, even if the same cohort of patients was used. No benefit would result in undertaking further small studies on this subject; one large study is needed. The emergence of neonatal networks should make this type of study a viable proposition.

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